SYNOPSIS

Clinical Study Report CN138003

TITLE OF STUDY: A Multicenter, Double-Blind, Randomized, Comparative Study of Aripiprazole and Olanzapine in the Treatment of Patients with Acute Schizophrenia

INVESTIGATORS AND STUDY CENTERS: This study was conducted by 119 primary investigators (342 investigators and sub-investigators) at 119 study centers in Australia, Austria, Belgium, Croatia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Portugal, Romania, Russia, South Africa, Spain, Sweden, Switzerland, and the United Kingdom.

PUBLICATIONS: None

STUDY PERIOD: Date first patient enrolled: 05-Jun-2000

Date last patient completed: 06-May-2002

CLINICAL PHASE: III

OBJECTIVES:

Primary: The co-primary objectives of this study were to compare the efficacy of aripiprazole versus olanzapine as measured by the Positive and Negative Syndrome Scale (PANSS) Total Score, and to compare the safety and tolerability of aripiprazole versus olanzapine as evidenced by significant ($\geq 7\%$) weight gain during treatment.

Secondary: The secondary objectives of this study were to compare the efficacy profiles of aripiprazole versus olanzapine based upon the results of efficacy scales (PANSS, Clinical Global Impression [CGI], and Montgomery-Asberg Depression Rating Scale [MADRS]), and to compare the safety and tolerability of aripiprazole versus olanzapine, and the response rate and discontinuation rate in patients having received aripiprazole versus olanzapine (responders are patients with a CGI Improvement (CGI-I) Score relating to very much or much improved, or with a decrease in PANSS Total Score of at least 30% from baseline).

Pharmacoeconomics and Outcomes Research: The objectives of pharmacoeconomics and outcomes research were to compare quality-of-life scores, overall health care resource utilization, and functional outcomes measures between treatment groups. Data from the pharmacoeconomics and outcomes research study will be reported at a later date in an addendum.

METHODOLOGY: This was a multicenter, randomized, double-blind, comparative study of aripiprazole (15 - 30 mg) and olanzapine (10 - 20 mg) in patients who were having an acute relapse of schizophrenia.

After informed consent was obtained, patients underwent a 2- to 7-day screening/psychotropic medication washout period (up to 14 days with permission from BMS). There was no requirement for patients to be hospitalized during this study. Patients who met criteria for inclusion were entered into an initial 6-week treatment period in which patients were randomized to double-blind aripiprazole or olanzapine at a 1:1 ratio. Patients started at the lowest dose of study medication: aripiprazole 15 mg or olanzapine 10 mg. At the end of Week 1, the aripiprazole dose could be increased to 20 mg and the olanzapine dose could be increased to 15 mg based on clinical judgment and a CGI-I Score of ≥ 3. At the end of Week 2, the aripiprazole dose could be increased to 30 mg and the olanzapine dose could be increased to 20 mg based on clinical judgment and a CGI-I Score of ≥ 3. Subsequent dose increases and decreases were allowed within dose ranges, based on efficacy and tolerability. The predetermined doses for the duration of the study were 15-, 20-, or 30-mg aripiprazole and 10-, 15-, or 20-mg olanzapine. Patients with a CGI-I Score of ≥ 4 and reduction of less than 20% on the PANSS Total Score at Week 6 were discontinued from the study. Patients unable to tolerate the lowest dose of study medication were discontinued from the study.

At the conclusion of the initial 6-week treatment period (Acute Phase), patients with a score of 1 - 3 on the CGI-I Scale or a reduction of at least 20% on the PANSS Total Score continued into an extended double-blind (15 - 30 mg aripiprazole or 10 - 20 mg olanzapine) treatment period, which could last up to a maximum of 140 weeks. Patients who maintained an appropriate clinical response could remain on treatment until approximately August 2003. Throughout the study, one-step dose reductions and increases were allowed based on tolerability and efficacy, respectively.

Analyses of the co-primary endpoints occurred at Week 26 and were presented in an interim report. In order to perform these analyses, the data was unblinded internally to a limited number of people at Bristol Myers Squibb Company (BMS). Treatment assignments remained blinded to investigators and patients until the database lock of the first 52 weeks of the study.

The Extension Phase results beyond 52 weeks will be presented in an addendum to this report.

NUMBER OF SUBJECTS/PATIENTS: A total of 750 patients were enrolled in the study. Of these, 703 were randomized to treatment: 348 to the olanzapine group and 355 to aripiprazole group. A total of 401 (57%) of the patients discontinued the study before Week 52: 183 (53%) of the olanzapine group and 218 (61%) of the aripiprazole group. Two patients in the aripiprazole group died during the study. Three hundred and two patients (43%) completed the study: 165 (47%) of the olanzapine group and 137 (39%) of the aripiprazole group.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients were required to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for acute schizophrenia and be in acute relapse. Patients must have had a previous response to a neuroleptic treatment other than clozapine.

In order to be randomized into the study, patients had to have a PANSS Total Score ≥ 60 and a score of ≥ 4 on two or more of the following PANSS items: delusions, hallucinatory behavior, conceptual disorganization, suspiciousness.

Patients had to have a CGI-I Score of 1 to 3 or a reduction of at least 20% on the PANSS Total Score at the Week 6 visit in order to continue into the extended treatment period.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Aripiprazole 5-mg tablets, one tablet daily, administered orally, batch numbers 99J84A005A and 00A75A005A; 10-mg tablets, 1 tablet daily, administered orally, batch numbers 98B85A010E, 99C77A010B, and 00F85A010; and 15-mg tablets, 1 tablet daily, administered orally, batch numbers 99H93A015B, 99H93A015A, and 99L77A015.

DURATION OF TREATMENT:

The total duration of treatment was up to 140 weeks (6 weeks initial Acute Phase treatment plus extended treatment up to 134 weeks). Patients could remain in extended treatment until approximately August 2003.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Olanzapine 5-mg capsules, 2, 3 or 4 capsules daily, administered orally, batch numbers M00007 and M00026; Zyprexa 5-mg tablet (open-label) 2, 3 or 4 tablets daily, administered orally, batch number A018116; placebo tablets, 1, 2 or 3 tablets daily, administered orally, batch numbers 98B85P000C, 98B85P000D, 99K77P000A, and 99K77P000B; placebo capsules, 2, 3, or 4 capsules daily, administered orally, batch numbers 99F081, 00F090, 00F091, 00F092, and 00F093,

CRITERIA FOR EVALUATION:

Efficacy: Efficacy rating scales completed during this study include the PANSS, CGI Severity of Illness (CGI-S) and CGI-I scales, and the MADRS. Response was defined as a $\geq 30\%$ decrease in the PANSS Total Score or a score of 1 or 2 on the CGI-I Scale.

Safety: Safety assessments include medical review of reports of AEs (including intercurrent illness), vital sign measurements, electrocardiograms (ECGS), body weight, concomitant medications, and results of physical examination and clinical laboratory tests. Extrapyramidal symptoms (EPS) rating scales completed during this study were the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Rating Scale.

Pharmacoeconomics and Outcomes Research: Pharmacoeconomic information collected during the study includes residence status and health care resource use. Outcomes research measures include the Patient Function Self-Report, Medication Adherence Scale (MAS), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

Statistical Methods: The co-primary outcome measures were the mean change from baseline to Week 6 (LOCF [Last Observation Carried Forward]) in the PANSS Total Score and the percentage of patients showing significant weight gain (a $\geq$ 7% increase) from baseline to Week 26 (LOCF). The co-primary outcome measure of the percentage of patients showing significant weight gain was added to the study after all patients were randomized, but approximately 12 months prior to the last patient last visit. The co-primary efficacy outcome measure of the mean change from baseline in PANSS Total Score at Week 6 was analyzed within the framework of Analysis of Covariance (ANCOVA). The analysis model included the baseline PANSS Score as a covariate and treatment as main effect. The primary presentation of results consists of the model-based estimates and the two-sided 95% confidence interval (CI) for the treatment difference (aripiprazole - olanzapine) constructed from the means and the standard error from the ANCOVA model. The upper bound of this 95% CI for the difference between the treatment groups was evaluated against the non-inferiority margin of 6 pre-specified in the protocol. The co-primary body weight outcome measure was assessed by the Cochran-Mantel-Haenszel (CMH) test stratified by prior olanzapine use (yes/no) and baseline body mass index (BMI) split into three groups: < 23, 23 - 27, and > 27 kg/m^2.

In order to control the overall type-I error rate (erroneously reject one of the two null hypotheses), the two stage Hochberg procedure was applied. The power to simultaneously show a true treatment difference of less than 6 in the mean change from baseline to Week 6 in the PANSS Total Score and to show a treatment difference in proportion of patients showing significant weight increase from baseline to Week 26 was calculated under the assumption that both primary endpoints are independent. The power was calculated as the product of the powers of the two tests.

The planned sample size of 620 evaluable patients (310 per treatment group) would yield 90% power to show that the true treatment difference (aripiprazole minus olanzapine) is less than 6 in the mean change from baseline to Week 6 in the PANSS Total Score (as evidenced by the upper bound of the 95% CI being less than 6). This sample size calculation is based on a non-inferiority one-sided test using the upper bound of the two-sided 95% CI, assuming a standard deviation for change from baseline to Week 6 in the PANSS Total Score of 23.

With 620 evaluable patients (310 per group), the power to show a true treatment difference of 15% in percentage of patients with significant weight gain is more than 99%. This assumes that 10% of aripiprazole patients and 25% of olanzapine patients show significant weight gain at Week 26 and that the testing is two-sided at the 0.05 significance level.

Given a total of 620 evaluable patients (310 per group), the power to simultaneously show a true difference (aripiprazole minus olanzapine) of less than 6 in the mean change from baseline to Week 6 in the PANSS Total Score and to show a true treatment difference of 15% in the percentage of patients with significant weight gain at Week 26 is greater than .9 x .99, ie, about 90%.

ANCOVA was used to evaluate the mean change from baseline to each specified visit in the following efficacy measures: mean change from baseline in PANSS Total Score, PANSS Positive Subscale Score, PANSS Negative Subscale Score, PANSS-derived BPRS Core Score, CGI-S of Illness Score, MADRS Total Score, and mean CGI-I Score. The analysis model included the baseline measure as a covariate and treatment as main effect. The percentage of responders (defined as a rating of very much improved or much

improved on the CGI-I Score or at least a 30% decrease from baseline in the PANSS Total Score) was analyzed within the framework of the CMH General Association Test.

The secondary outcome measures were the mean change in patient weight from baseline to Week 26 and the mean percent change in patient weight from baseline to Week 26. The secondary outcome measures were evaluated by analysis of covariance (ANCOVA), adjusting for baseline weight and controlling for prior olanzapine use.

The Safety Sample included those patients who received at least one dose of study medication as indicated on the dosing record. The Efficacy Sample included those patients in the Safety Sample who had at least one on-study efficacy scale (psychiatric scale) evaluation (ie, evaluable patients). Patients who had not been treated for at least 14 days as indicated on the dosing record or were missing baseline or on-study weight measurements were excluded from the weight analyses. The mean change from baseline for the OC data set and separately for the mean change from baseline to maximum on-treatment evaluation and Week 52 LOCF data, for serum prolactin, glucose, glycosylated hemoglobin, LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides were analyzed using ANCOVA, adjusting for baseline value and fasting status and controlling for treatment group. The same analyses were done without controlling for fasting status for data collected in the fasting state.

In both safety and efficacy analyses the LOCF data set was considered the primary data set. The Observed Cases (OC) data set analyses were performed to corroborate the results of the LOCF analyses.

CO-PRIMARY RESULTS: This study had two co-primary objectives. One objective was to compare the efficacy of aripiprazole versus olanzapine as measured by the PANSS Total Score after 6 weeks of treatment. At Week 6 (LOCF), patients in both treatment groups improved on their mean change from baseline PANSS Total Score (-27.36 and -22.15 points in the olanzapine and aripiprazole groups, respectively). The mean difference in improvement between olanzapine and aripiprazole groups was 5.21 points. The upper bound for the CI of treatment difference was 8.25, exceeding the pre-specified upper bound limit of 6 to test non-inferiority. Therefore, this study failed to meet the criterion for non-inferiority.

The other objective was to compare the safety and tolerability of aripiprazole to olanzapine as evidenced by significant ($\geq$ 7% increase from baseline) weight gain following 26 weeks of treatment. At Week 26, a clinically significant higher proportion of patients in the olanzapine group experienced clinically significant ($\geq$ 7%) weight gain than in the aripiprazole group (31.5% and 12.5% in the olanzapine and aripiprazole groups, respectively). This difference between treatment groups was statistically significant (p < 0.001).

EFFICACY RESULTS: At Week 6 (LOCF), statistically significant differences in favor of the olanzapine group were also observed in the mean change from baseline in the CGI-S Score, PANSS-Positive Subscale Score, PANSS-Negative Subscale Score, PANSS-derived BPRS Core Score, and MADRS Total Score. In addition, statistically significant differences in favor of the olanzapine group were demonstrated in the mean CGI-I Score and the percentage of responders at Week 6.

At Week 6 (OC), however, statistically significant differences in favor of the olanzapine group were demonstrated in the mean change from baseline in only the PANSS Total Score, CGI-S Score and MADRS Total Score. The mean change from baseline to Week 6 in the PANSS-Positive Subscale Score, PANSS-Negative Subscale Score, PANSS-derived BPRS Core Score, and the Week 6 mean CGI-I Score and the percentage of responders were not statistically significant.

For the PANSS Total Score, statistical differences favoring olanzapine were seen in the LOCF dataset in the Extension Phase (Weeks 8-52), while no significant differences were observed in the OC analyses (Weeks 8-52). By design, patients who did not have a CGI-I Score $\leq$ 3 or a PANSS Total Score improvement of $\geq$ 20% from baseline were excluded from the outpatient double-blind Extension Phase. Consequently, of the randomized patients, 74% of the olanzapine patients and 65% of the aripiprazole patients entered the Extension Phase. The efficacy scores for these partial responders, who were discontinued from the study per protocol, were also carried forward to Week 52, and contributed to the differences in efficacy observed between the two treatment groups after Week 6 on the LOCF analysis. Given the large amount of imputed LOCF data, the large amount of missing data in the OC dataset, and the

lack of corroboration between the LOCF and OC analyses, the results of the efficacy analyses for time points beyond Week 6 were difficult to interpret.

In a prespecified analysis that linked efficacy and weight gain, the percentage of patients who were in response on treatment without having significant weight gain was similar for the olanzapine and aripiprazole groups at Weeks 6, 26, and 52.

SAFETY RESULTS: The aripiprazole group showed statistically superior results on the secondary outcome measures regarding weight. Specifically, the treatment differences in the mean change from baseline in patient weight and in the percentage of patients showing significant weight gain during the trial were statistically significant in favor of the aripiprazole group. In a post-hoc analysis, a statistically significant difference in the change in mean body weight gain between olanzapine and aripiprazole was observed in all cohorts stratified by patients' baseline BMI (ie, BMI < 23, 23 – 27 and > 27 kg/m^2).

Mean total cholesterol, LDL-cholesterol and triglycerides levels decreased in the aripiprazole group and increased in the olanzapine group at all time points to Week 52 in both the LOCF and OC analyses. The differences in mean change from baseline to Week 52 (LOCF) in these levels for patients treated with olanzapine and aripiprazole were statistically significant in favor of aripiprazole. Olanzapine was associated with significantly greater incidences of new onset of hypercholesterolemia, new onset of LDL elevations, and new onset of hypertriglyceridemia. Serum glucose levels and glycosylated hemoglobin levels decreased in both treatment groups.

Mean reductions from baseline in serum prolactin were significantly greater in the aripiprazole treatment group compared with the olanzapine treatment group at all time points (OC) and at Week 52 (LOCF). A considerably larger proportion of patients in the olanzapine treatment group than in the aripiprazole treatment group (47.1% versus 9.3%) had abnormal prolactin levels during the study. In those patients whose prolactin values at baseline were normal, the proportion of patients with abnormal prolactin levels on treatment was statistically significantly higher in the olanzapine treatment group than in the aripiprazole treatment group. In addition, in those patients with abnormal prolactin values at baseline, the proportion of patients without abnormal prolactin levels on treatment was statistically significantly higher in the aripiprazole treatment group than in the olanzapine treatment group.

There was no significant difference between treatment groups with respect to AIMS Total Score at Week 52. Statistically significant treatment differences were seen in favor of olanzapine in mean SAS Total Score and in Barnes Akathisia Global Clinical Assessment at Week 52 (LOCF). However, the baseline scores and the differences between the treatment groups were small. More EPS-related adverse events occurred in the aripiprazole group than in the olanzapine group. The most common EPS-related adverse event in both groups was akathisia. However, EPS-related adverse events rarely led to discontinuation from the 52 week study (1% of olanzapine treated patients and 2% of aripiprazole treated patients). More aripiprazole patients received concomitant anticholinergic medications (16%) than olanzapine patients (9%).

Aripiprazole was generally safe and well tolerated in this study. The overall incidence and rates of individual AEs were similar between the aripiprazole and olanzapine groups. The AEs with rates ≥ 10% in at least one treatment group were weight gain (21% in olanzapine-treated patients and 6% in aripiprazole treated patients), insomnia (21% in olanzapine-treated patients and 27% in aripiprazole treated patients), headache (8% in olanzapine-treated patients and 15% in aripiprazole treated patients), anxiety (13% in olanzapine-treated patients and 16% in aripiprazole treated patients) and somnolence (11% in olanzapine-treated patients and 4% in aripiprazole-treated patients). The only SAEs ≥ 5% in either treatment group were both related to the underlying disorder: hospitalization for psychosocial support (2% in olanzapine-treated patients and 6% in aripiprazole-treated patients) and reaction schizophrenic (5% in both treatment groups). Reaction schizophrenic was the only AE leading to discontinuation of study therapy with a rate ≥ 5% in either treatment group (4 % in olanzapine-treated patients and 6% in aripiprazole-treated patients).

In all, 29% of the randomized patients in the aripiprazole group and 22% of the randomized patients in the olanzapine group discontinued before Week 6. The discontinuation rate over time was statistically significantly higher in the aripiprazole group than in the olanzapine group for the period up to Week 52. The treatments groups separated at Week 6 in terms of discontinuations; beyond Week 6 dropouts were comparable.

In this study, 61.4% of the randomized patients in the aripiprazole group and 52.6% of the randomized patients in the olanzapine group discontinued the study before Week 52. More patients in the aripiprazole group (19.2%) than in the olanzapine group (14.9%) discontinued before Week 52 for reasons of adverse event. There were two deaths but neither was considered related to study drug.

Apart from the incidences of potentially clinically significant weight increases which occurred in 42% of olanzapine-treated patients and in 18% of aripiprazole-treated patients, the incidences of vital sign abnormalities were similar between the two treatment groups. Also the incidences of potentially clinically significant ECG abnormalities were similar between the two treatment groups.

CONCLUSIONS:

- This study had two co-primary objectives. One primary objective was to compare the efficacy of aripiprazole versus olanzapine as measured by the PANSS Total Score after 6 weeks of treatment (LOCF). Both aripiprazole and olanzapine demonstrated efficacy for the treatment of patients with acute schizophrenia. However, the study failed to demonstrate that aripiprazole was non-inferior to olanzapine as measured by the mean change from baseline on the PANSS Total Score at Week 6. The olanzapine group experienced statistically significant greater improvement than the aripiprazole group in the Week 6 primary efficacy endpoint

- The second primary objective was to compare the safety and tolerability of aripiprazole to olanzapine as evidenced by significant ($\geq 7\%$) weight gain following 26 weeks of treatment. At Week 26 (LOCF), significantly more patients in the olanzapine group experienced clinically significant ($\geq 7\%$) weight gain than in the aripiprazole group

- At Week 6 (LOCF), statistical differences in favor of olanzapine were observed in the change from baseline in the PANSS Total Score, CGI-S Score, PANSS-Positive Subscale Score, PANSS Negative Subscale Score, PANSS-derived BPRS Core Score, and MADRS Total Score. In addition, statistical differences in favor of the olanzapine group were demonstrated in the CGI-I Score and the percentage of responders at Week 6. The OC analyses for PANSS Total Score, PANSS-Positive Subscale Score, PANSS-Negative Subscale Score, CGI-S Score, and percentage of responders were not statistically significant after Week 6. Beginning at Week 8 and continuing through Week 52, there were no statistical differences in the PANSS Total Score between treatment groups by OC analysis

- The percentage of patients who were in response, on treatment, without having significant weight gain was similar for the olanzapine and aripiprazole groups at Week 6, 26 and 52

- At Week 26 (LOCF), statistically significant differences in favor of aripiprazole were observed in the mean change from baseline in weight and in the percentage of patients showing significant weight gain. In a post-hoc analysis, a statistically significant difference between the change in mean body weight gain between olanzapine and aripiprazole was observed in all cohorts stratified by patients' baseline BMI. Statistically significant differences were also observed in total cholesterol, LDL-cholesterol, triglycerides, and prolactin levels among patients treated with aripiprazole compared to olanzapine

- No clinically relevant differences in vital signs or ECG findings were identified between treatment groups

- More EPS-related adverse events occurred in the aripiprazole group than in the olanzapine group. However, EPS-related adverse events rarely led to discontinuation from the 52 week study

- Aripiprazole was generally well tolerated as demonstrated by a comparable AE profile as olanzapine

- In post-hoc analyses of patients who responded during the first 6 weeks of treatment and entered the Extension Phase, aripiprazole had similar efficacy to olanzapine beginning at Week 8 and continuing through Week 52 in both the LOCF and OC analyses.

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